MEDICAL PRACTICE

Contemporary Themes

Benzodiazepine withdrawal: an unfinished story

HEATHER ASHTON

"I am 39 years old, married, with two children aged 18 years and 14 years. The younger was a very active baby, and when he was 18 months old I mentioned to the doctor that he was sleeping very little and though he did not seem tired in any way, I certainly was! After a course of vitamins I still felt worn out and this was when I was first prescribed Valium.

"This was 1971; I was then 27 years old. I remember instantly feeling a lot better—all the irritability and tiredness seemed to disappear and I became a lot more relaxed and content. The next three years seemed to fly over; the eldest child began school, my husband gained promotion, and we bought a new house. Any problems which cropped up during this time could always be wiped out just by taking a Valium. Life was pretty good! Moving house also meant changing doctor and this doctor was not very keen on repeating the monthly prescription on which I had come to depend. 'You must cut them down,' she said, 'three years is far too long.' I agreed wholeheartedly, 'Why not,' I thought, 'I don't need them now.' ... The youngest was at school and slept soundly—in fact had done for a long time. I started reducing the tablets and can honestly say I felt no ill effects.

"During this time my life hit an emotional crisis but this time, unlike in the past, I did not have the pills to cover it up. In January 1975 I suffered a miscarriage and after this, together with the conflict in my personal life, I visited the doctor in tears. She immediately put me back on Valium, this time increasing the dosage. Although the world was not as rosy as it was before, at least it was bearable. I did not realise then that this was the beginning of a new road to despair, mental and physical pain, and nearly complete disaster.

"My problems did not go away like in the early days on the pills—they seemed greater. I started to become withdrawn, insecure, and confused and suffered bouts of depression together with uncontrollable outbursts of rage. My digestive system seemed to be affected and this resulted in many visits to the hospital for the necessary tests. Some days were worse than others—sleep was no longer a welcome relief; I would lie awake in the middle of the night soaking in perspiration and feeling very ill. When sleep did come it was full of vivid dreams. The traumatic experiences in my life did not stop either, in fact they seemed greater than ever. One day I could cope no longer and the doctor recommended a top psychiatrist. This seemed the most logical solution at the time, so I agreed. It was diagnosed as endogenous depression and acute anxiety. During the following months I was prescribed many different forms of antidepressants, hypnotics, and tranquillisers to take with the Valium. None of these had any lasting good effects, in fact I gradually became worse instead of better. The relationship between our GP and myself broke down, making it necessary to change doctors. I became very paranoid and believed it was me against the world. During this time I contracted chickenpox quite badly which unfortunately caused a longstanding eye complaint to flare up. This was the start of the blackest period of my life, and by this time I felt as though I was bordering on insanity. During one particular bad spell my husband dragged me to the psychiatric inpatients, and here I saw a young doctor who told me it was not the pills I needed but psychotherapy. The pills were only covering up the mental turmoil.

"The next year involved extensive analysis and although at times this was mentally distressing, it seemed to help. During the weekly sessions it was suggested I drop my dose of Valium so I quickly agreed; at first it was easy—a bit jumpy when I dropped 1 mg—but then things became much worse. My confidence began to wane dramatically—I could not go out or be left on my own. My husband finally had to give up his job, as I spent most of the time begging him to come home as I was frightened. I started to feel very ill, and even going to the shops was a mammoth task. My doctor advised me not to drop the Valium any more (I was down from 15 mg to 4 mg) as I was suffering from chronic anxiety and needed some form of sedation. What both of us did not realise was—I was in tranquilliser withdrawal.

"The following year was hell for me and my family. I developed into a mental and physical wreck—suicidal thoughts were never very far away.

"In July this year I begged the doctor to help me—I could not go on any more like this—it was like a 'living death.' He suggested another form of tranquilliser and took the remaining Valium away—I thought I had gone mad. In sheer desperation I remembered a newspaper article about a group of people who suffered from tranquilliser side effects and withdrawal. I made a phone call, which

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was the most important call of my life; I was on the verge of madness and could they help?

"That was nine weeks ago and during that time I have not touched a tablet. This brought on a series of symptoms that I had experienced only mildly before. Noises jarred every fibre in my body and my eyes seemed to shun the light of day. I shook from head to foot and enormous panic attacks would sweep through my body, leaving me exhausted and totally afraid. Complete fatigue took over the feeling of tiredness and sleep no longer came with the night. Many times I thought it would be best to die.

"I am lucky to have found somewhere where sufferers can be encouraged and supported through withdrawal. I have found many new friends, who, like me, were caught up in the web of addiction. Also I have the good fortune to have a very caring and warm doctor to help me through this withdrawal. It has not been easy—it has been one of the hardest jobs of my life and it is not finished yet. In the early days I began to think I had gone mad, but gradually a new world is emerging. A world that is not covered over with pills. It can be a very frightening place until my mind becomes adjusted to its colours, noises, and pictures once more.

"Someone once wrote 'Tranquillisers are the anaesthetics of the emotions'; this is true. When used properly, they are a 'must' in medicine, but used over the long term they poison the body and destroy the mind. One day doctors will realise the extent of tranquilliser withdrawal syndrome but until then it is going to be a hard battle, but in the end, we sincerely hope, worth it."

Introduction

Evidence is rapidly accumulating that benzodiazepines are potentially drugs of dependence, that chronic use is associated with adverse effects, and that withdrawal may produce a definite abstinence syndrome.[1-6] As benzodiazepine dependence, with all its sequelae, is mainly iatrogenic, probably of large proportions,[5-7] it is of considerable medical importance.

Clinical experience with 12 consecutive patients who requested withdrawal from benzodiazepines is reported here.

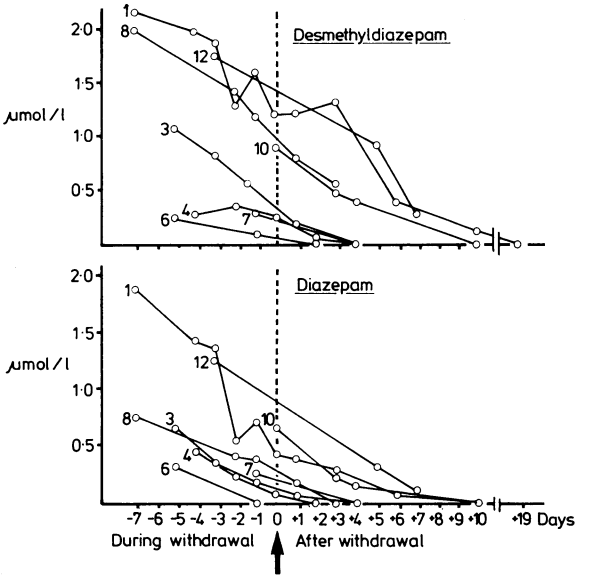
Patients and methods

The 12 patients (10 women and 2 men, aged 31 to 72) were referred by their general practitioners. The patients had become aware of the possibility of tranquilliser dependence through their own experiences, the press, or a lay tranquilliser withdrawal support group, and all actively requested help with withdrawal. All had taken only prescribed therapeutic doses of benzodiazepines; all had suffered adverse effects which they attributed to the drugs; and most had attempted unsuccessfully to cut down or withdraw completely.

Table I gives further details of the patients. The personal account (above) is typical of many reports in the medical and popular press. Only two patients had a definite history of psychiatric disorder before using benzodiazepines. Inquiries of close relatives in nine of the remaining cases showed that the patients had been considered "normal" and "stable" before benzodiazepines were prescribed.

METHOD OF WITHDRAWAL

The final withdrawal in all cases was from diazepam and patients taking other benzodiazepines were changed over to it. Usually this meant a progressive switch from lorazepam, 10 mg



Plasma concentrations of desmethyldiazepam and diazepam during and after withdrawal of diazepam in eight patients. Numbers refer to case numbers (see table I).

Conversion: SI to traditional units—Desmethyldiazepam: 1 μmol/l ≈ 271 μg/l. Diazepam: 1 μmol/l ≈ 285 μg/l.

TABLE I—*Details of 12 patients withdrawn from benzodiazepines at their own request*

Case No	Sex	Age	Reason for starting benzodiazepines	Duration of benzodiazepine use	Previous psychiatric illness	Psychotropic drugs used	Duration of follow up
1	F	34	Dysmenorrhoea	14 years	No	Diazepam Lorazepam Nitrazepam Antidepressants	6 months
2	M	31	Tinnitus	3 years	No	Lorazepam	6 months
3	F	50	Dizzy turns	10 years	No	Diazepam	4 months
4	F	43	Anxiety, depression	10 years	No	Diazepam Lorazepam Antidepressants	4 months
5	F	39	Disturbed nights (hyperactive child)	12 years	No	Diazepam Oxazepam Antidepressants	4 months
6	F	46	Postoperative shock	10 years	?No	Diazepam Clobazam Flurazepam Alprazolam	3 months
7	M	72	Backache	5 years	No	Lorazepam	3 months
8	F	54	Anxiety, depression	22 years	Yes	Chlordiazepoxide Diazepam Antidepressants	3 months
9	F	42	Neck pain	18 years	No	Diazepam Flurazepam Prazepam Antidepressants	2 months
10	F	67	Depression	4 years	Yes	Lorazepam Antidepressants	2 months
11	F	36	After influenza	3 years	No	Lorazepam Triazolam Chlordiazepoxide Antidepressant	1 month
12	F	46	Headaches	14 years	No	Diazepam Lorazepam	1 month

TABLE II—*Major symptoms reported by patients before and after benzodiazepine withdrawal*

Symptoms	At presentation (n = 12)		0-2 weeks (n = 12)		3-5 weeks (n = 12)		6-12 weeks (n = 10)		13-27 weeks (n = 5)	
	No	Severe*	No	Severe*	No	Severe*	No	Severe*	No	Severe*
Psychological										
Drowsiness, fatigue	9	6	5	5	5	3	3	2	2	1
Excitability	9	8	8	7	7	9	5	2	2	
Unreality, depersonalisation	10	8	9	6	6	2	3	1	1	
Poor memory, concentration	12	11	11	12	8	10	6	3	2	1
Perceptual distortion	6	5	8	7	5	4	1		1	
Hallucinations	4	1	2	1	1	1	1		1	
Obsessions	4	1	2	2	2	2				
Agoraphobia, phobias	11	7	11	11	6	6	4		1	
Panic attacks	11	7	11	8	4	6	3	1	2	2
Depression	12	4	12	8	6	5	4	1	3	
Paranoid thoughts	2	1	6	3	4	2				
Rage, aggression	3	1	5	4	3	3	1			
Craving	10	9	3	2	1	1	1		1	
Somatic										
Central nervous system:										
Headache	9	7	11	7	6	6	4	2	1	
Pain (limbs, back, neck)	10	9	8	4	7	5	5	3	3	1
Pain (teeth, jaw)	6	5	4	3	3	2	3			
Paresthesiae (limbs, face)	10	5	12	9	9	9	5		1	1
Stiffness (limbs, back, jaw)	8	5	9	4	6	3	3	2		
Weakness	9	8	10	9	6	7	4		2	2
Tremor	8	7	9	4	7	4	5	1	2	
Muscle twitches, fasciculation	6	6	8	7	7	6	4	2	3	
Ataxia	8	8	12	12	6	7	4		3	
Dizziness, lightheadedness	9	7	10	7	7	4	5	2	1	
Blurred or double vision	8	6	9	6	7	5	5	2	3	
Tinnitus	7	6	9	6	6	4	5		1	
Speech difficulty	7	6	10	6	6	4	4	2		
Hypersensitivity (light, sound, taste, smell)	10	10	10	10	7	9	5	2	3	
Insomnia, nightmares	8	4	10	10	8	8	4	2	3	2
Fits†	1	1	1		1		1		1	
Gastrointestinal:										
Nausea, vomiting	8	4	5	3	3	1	1		2	1
Abdominal pain	10	4	7	4	4	3	1	1	1	
Diarrhoea or constipation	6	5	7	5	5	2				
Appetite, weight change	6	5	8	5	7	5				
Dry mouth	10	5	8	8	5	5	5	2	3	2
Metallic taste	7	4	8	6	5	1	5	2	1	
Dysphagia	1	1	2	1	4	1	1		1	
Cardiovascular or respiratory:										
Flushing, sweating	9	5	10	7	6	7	5	2	1	
Palpitations	8	7	9	7	5	3	3	1	2	
Overt hyperventilation	3		3		1	1			1	
Urogenital or endocrine:										
Thirst	5	5	6	4	4	2	5		1	1
Frequency, polyuria	8	7	8	5	2	4				
Incontinence	4		5							
Menorrhagia (n = 8)	5	5	4	2						
Mammary pain or swelling			7	1						
Miscellaneous:										
Rash/itching	6	4	5	4	4	5	1		1	
Stuffy nose, sinusitis	4	3	7	5	3	2	1		1	
Influenza-like symptoms			10	7	2	1				

*Number of patients rating symptoms as moderate or severe (number and severity of symptoms may have been alleviated by treatment, especially in first six weeks).
†One patient (case 1) had ?temporal lobe epilepsy. None had major convulsions.

diazepam being substituted for every 1 mg lorazepam, changing one dose each day. Diazepam dosage was then reduced on successive days from 10 to 8 to 6 to 5 to 4 to 3 to 2 to 1 mg, administered two or three times daily, depending on the benzodiazepine dosage before withdrawal. When benzodiazepines had also been prescribed as hypnotics (flurazepam, nitrazepam, triazolam), these were stopped immediately and a non-benzodiazepine hypnotic used temporarily instead (see below). Benzodiazepines were usually totally withdrawn within two weeks.

Nine patients were admitted to a clinical pharmacology ward (Freeman Hospital) and in eight plasma concentrations of diazepam and desmethyldiazepam were measured during and after withdrawal (figure). The duration of hospital stay was three to four weeks. In the other three patients, managed as outpatients, plasma concentrations were not monitored.

OTHER TREATMENT

I visited patients in hospital daily (six or seven days a week), listened sympathetically to their complaints, and gave simple reassurance. Care was taken not to suggest symptoms, which were recorded independently (see below). Outpatients were seen at least twice a week for the first month. Thereafter all patients were followed up at weekly or fortnightly intervals for up to six months.

Major symptoms were treated where possible. For insomnia a rotation of hypnotics was used, a different hypnotic being given each night. The hypnotics included: promethazine (75-100 mg), dichloralphenazone (1·3-1·95 g), chlormethiazole (two capsules, 384 mg base), and butobarbitone (100-200 mg). Six of the 12 patients took hypnotics regularly for the first four to six weeks after withdrawal; two took them occasionally. Thereafter the hypnotics were withdrawn gradually. Other drugs were used as follows: propranolol (40 mg three times a day) for tremor, muscle fasciculation, or myoclonic jerks (four patients); clonidine (100 μg twice a day) for panic (four patients for two weeks); and haloperidol (4-7·5 mg daily) for hallucinations, intrusive thoughts, or as an anxiolytic (three patients). One patient (case 1) with "fits" (?temporal lobe epilepsy) took carbamazepine (400-600 mg daily). Four patients who were depressed were given antidepressants: amitriptyline (50-75 mg daily), nortriptyline (10 mg three times a day), or mianserin (30-60 mg daily), but antidepressants were withdrawn from all patients after six to eight weeks except in case 10. Two patients received buprenorphine (100-200 μg) for severe pain, and three received dicyclomine hydrochloride (10 mg three times a day) for "irritable colon" symptoms.

Of non-pharmacological measures, two patients used transcutaneous electrical nerve stimulation for abdominal pain and two had hypnosis for relaxation.

SYMPTOMS AND CLINICAL COURSE

Symptoms were recorded formally using a checklist of 55 symptoms initially compiled after experience with other patients. New symptoms were added to the list when volunteered by the present patients. The checklist was administered weekly

by house physicians unfamiliar with benzodiazepine withdrawal. Patients rated each symptom on a scale in which 0=none; 1=mild; 2=moderate; 3=severe. Table II gives details of the main symptoms.

All the patients had many symptoms when first seen; these had arisen either during benzodiazepine treatment or during their own attempts to reduce dosage or stop benzodiazepines. The clinical picture changed little during the changeover to diazepam or during its withdrawal; nevertheless, the symptoms increased in severity or new symptoms developed about five to seven days after diazepam was stopped. Thereafter, the symptoms waxed and waned—a variability that is not apparent in table II, which gives mean symptom ratings for the whole group of patients.

The duration, frequency, and severity of symptoms decreased with time, with a general tendency towards slow improvement. Two patients (cases 4 and 2) were almost entirely free of symptoms four and six months after withdrawal, and nine have shown moderate or definite improvement after one to six months. One patient (case 10) still has severe anxiety and depression, which was present before and during benzodiazepine treatment, and transferred to another hospital six weeks after withdrawal. Otherwise, all patients are glad to be off their drugs and none have relapsed.

All patients had a similar range of symptoms, and, remarkably, used the same phrases at the first interview to describe their sensations. Common phrases included: "I feel as though I am walking on cotton wool"; "I feel as though there is a mist/net curtain/veil over my eyes"; "My head feels as though it is stuffed with cotton wool"; "The walls/floor seem to be sloping and television pictures look 3-D"; "I feel that I am going crazy"; "Everything feels unreal/distant; I feel I am not really me"; "My head feels like a huge balloon/football."

Many symptoms were similar to those in anxiety neurosis or during withdrawal from other central nervous system depressants that produce dependence. Certain symptoms, however, appear to form part of a cluster characteristic of the benzodiazepine withdrawal syndrome.

"PSYCHOLOGICAL" SYMPTOMS

Perceptual distortion, hallucinations, delusions—Most patients complained of perceptual distortion (see quotations above). Three patients had visual hallucinations—for example, seeing disembodied faces—some heard bangs and thumps or tunes, and many were aware of misinterpreting the environment—for example, a coat hanging on the door would appear to be a person. Several felt that their body was distorted.

Paranoid thoughts and feelings of persecution occurred in more than half the patients, who reported strong ideas that people were talking about them, plotting ways to discomfort them, and laughing about them behind their backs. These symptoms disappeared about four weeks after withdrawal.

Unreality, depersonalisation—Over three quarters of the patients complained of disturbing feelings of unreality or depersonalisation. This was a major cause (along with loss of memory and concentration) of the commonly expressed fear of going mad and improved after withdrawal; many patients described "windows," when they felt themselves again for some hours or days. The "windows" lasted for successively longer periods but even months after withdrawal could suddenly be replaced by renewed periods of depersonalisation.

Agoraphobia—Eleven of the 12 patients developed agoraphobia while taking benzodiazepines. Six were completely unable to go out of the house alone and others had to overcome feelings of panic to do so and were not always successful. Sometimes they would "freeze" with panic while out. Five patients had had unsuccessful psychiatric treatment for agoraphobia with drugs, psychotherapy, or behaviour therapy. This symptom improved remarkably, however, with no other treatment but benzodiazepine withdrawal. At present four of the six patients with severe agoraphobia can go shopping, visit neighbours, or attend the outpatient clinic entirely alone, and agoraphobia is no longer a problem in the less severely affected patients.

Depression—Depression was common during benzodiazepine use and seven patients had also been treated with antidepressants. Although all patients complained of depression during withdrawal, only one (case 10), with a history of depression, was continuously depressed. In the others depression could be noticeably alleviated by talking about problems and receiving reassurance. Many of them described their depression as "coming on in waves" several times a day or week. Between such "waves" they could behave normally and enjoy certain activities. Occasionally feelings of "high" or exhilaration were experienced about three or four weeks after withdrawal. "Emotional anaesthesia," inability to feel pleasure or pain, was described only by the two patients with a psychiatric history (cases 8 and 10), although several patients remarked that they could not cry.

Craving—Although before withdrawal all the patients taking lorazepam had a craving for the drug (in that they could not get through the day without their tablets), this feeling was mostly absent during the changeover to diazepam and was rare during and after withdrawal. The same was true in those patients who had previously felt that they could not get through the night without their regular benzodiazepine hypnotic. Only one patient (case 1) still reports a craving for nitrazepam. None of the patients have started taking benzodiazepines again, despite continuing symptoms, and in fact they regard tranquillisers as distasteful. None have replaced benzodiazepines with other drugs or with alcohol; all the 10 smokers in the group reported a temporary dislike of cigarettes and a sharp drop in consumption during the first two weeks of withdrawal. Their consumption of cigarettes then increased for several weeks but tended to return to prewithdrawal levels as symptoms disappeared.

SOMATIC SYMPTOMS

Paresthesiae—All patients had feelings of "pins and needles," tingling, "crawling in the skin," numbness, or altered sensation at some time. Usually affecting the limbs in a glove and stocking distribution, the sensations also occurred often around the mouth, jaw, and tongue. Paresthesiae waxed and waned, altered distribution, and sometimes disappeared during the course of a day. No objective abnormal neurological signs were found except in one patient (case 8) with ?multiple sclerosis. Paresthesiae were present in the absence of overt hyperventilation, which was observed briefly in three patients during panic attacks but was not an obvious feature throughout withdrawal. Paresthesiae also persisted in many patients after panic attacks had disappeared.

Pain in various parts of the body was prominent. Neck pain and occipital headache, pain in the limbs described as aching, bursting, or cutting, and pain in the jaw were all common and often severe. Many patients complained of toothache, and some had undergone extractions of apparently normal teeth. Edentulous patients also complained of "toothache." All patients at some stage complained of a metallic or unpleasant taste. Stiffness and weakness often accompanied the neck, limb, and jaw pains. Tremor of the hands and jaw, and muscle fasciculation, particularly in the thighs, were noted in several patients; many complained of sudden jerks, particularly in the legs but sometimes affecting the shoulders and back. Myoclonic jerks were observed in several patients.

Ataxia—All patients complained of difficulty in walking. This appeared to result from a combination of sensory disturbance, muscle weakness, pain and stiffness, and perceptual disturbances.

Visual disturbances—Blurring of vision and double vision were common; several patients had changed their spectacles with no improvement. Most of these patients complained that

they felt they were seeing the world through a mist or veil and had great difficulty in reading. Photophobia, along with increased sensitivity to noise, taste, and smell, was also very common.

Gastrointestinal symptoms—A high proportion of patients complained of gastrointestinal symptoms, including dysphagia, nausea and vomiting, abdominal pain, diarrhoea, and constipation. Five patients had had gastrointestinal investigations and had been told that they had "irritable bowel syndrome." These symptoms disappeared completely or improved after benzodiazepine withdrawal in all but one of the patients. Several patients lost over 5 kg in weight.

Influenza-like symptoms—Ten patients developed an influenza-like illness with prostration, weakness, and postural dizziness, aches and pains in muscles and joints, stuffy nose, and sinus pains, but no fever. These symptoms appeared within the first two weeks of withdrawal, lasting from a few days to four weeks. Two patients recognised the symptoms from previous attempts at self withdrawal, when they had been diagnosed as having sinusitis.

Metabolic and endocrine symptoms—Menorrhagia occurred during chronic benzodiazepine use in five of the nine premenopausal women but tended to improve after withdrawal. Six women remarked on breast pain and engorgement during withdrawal and one man also complained of mammary pain. Loss of appetite and weight were common in early withdrawal; three patients noted a "voracious" appetite for a short period about three weeks after withdrawal, and several patients gained up to 4 kg in weight. Increased thirst with polyuria was common in early withdrawal, occurring in over half of the patients, and accompanied by occasional urinary incontinence in four. These symptoms subsided after a few weeks.

Discussion

The features of benzodiazepine withdrawal appear to constitute a new syndrome characterised by a particular cluster of symptoms and a protracted clinical course. The cluster is unusual in anxiety states,[8] and both Owen and Tyrer and Petursson and Lader have noted that the symptoms are qualitatively different from those in anxiety neurosis.[3 5] In addition the course of the benzodiazepine withdrawal syndrome appears to be much longer than that of other drugs of dependence, and in particular longer than that reported for benzodiazepines, which has been stated to last 5-15 days,[5] 2-4 weeks,[3] and 10-54 days.[4] Nevertheless, although improved, most of my patients were still not free of symptoms four to six months after withdrawal, and interviews with other patients suggest that complete recovery may take a year or more. The duration, course, and incidence of recovery is ill documented in medical reports, and further studies on this aspect are badly needed. Furthermore, it is not known, despite various estimates,[3 5 7 9] what proportion of patients taking benzodiazepines become dependent, or what determines whether or not they do.

Clearly benzodiazepine dependence is not confined to patients with a history of psychiatric disorders. Only two of the 12 patients studied had definite psychiatric problems before starting taking regular benzodiazepine treatment (cases 8 and 10), and only one (case 4) was aware of being prescribed benzodiazepines for a "nervous complaint." The others had mainly somatic symptoms, although their medical practitioners may have ascribed these to anxiety. Close relatives, however, described these patients as normal and stable before benzodiazepine use.

Nor does there appear to be a necessary connection between dependence on benzodiazepines and dependence on other drugs, as has been suggested.[10] Although 10 of the 12 patients were smokers, none drank more than social amounts of alcohol; none had a history of dependence on other drugs; none had abused benzodiazepines or raised their dosage above the prescribed levels (in fact, most had attempted to reduce dosage); and none replaced benzodiazepines with other drugs after withdrawal. The absence of craving was a notable feature during and after withdrawal. All patients were relieved at being free from the need to go on taking drugs, which they felt were distasteful. It would appear from the patients' attitude that there is little likelihood of relapse. Long term studies are needed to establish this point.

Possibly individuals with certain personality characteristics are more likely than others to be prescribed benzodiazepines. In a recent questionnaire study of an Oxford University student population aged 18-20, Golding *et al* found that a history of having taken hypnotics or tranquillisers for more than two consecutive days correlated significantly with a high neuroticism and low extraversion score on the Eysenck personality questionnaire,[11] the incidence of such drug use being more than 10% overall in the sample of 178 students.[12] Similar results have recently been obtained among 112 Newcastle University medical students (unpublished observations). In the present series of patients, neuroticism scores on the Eysenck personality questionnaire were also high (mean neuroticism score (SD) 17·63 (5·75), compared with 9·83 (5·18) for men and 12·74 (5·20) for women in the normal population.[12] This test is claimed to measure trait rather than state anxiety, but the presence of withdrawal symptoms may nevertheless have influenced the scores.

It is impossible to say whether the previously apparently stable patients would have developed psychiatric symptoms in the absence of benzodiazepine treatment. Nevertheless, the initial appearance of symptoms after a period of regular benzodiazepine use, the fact that all patients developed similar symptoms irrespective of the psychiatric history, and the improvement after drug withdrawal, all suggest that the symptoms resulted from benzodiazepine use and not from an underlying anxiety neurosis. This view has also been expressed by Lader, Tyrer, and others.[1-6]

The appearance of symptoms while the patients were still taking benzodiazepines suggests the development of tolerance. Symptoms of prolonged use are said to include loss of concentration and memory, decline in psychomotor performance, depression, and emotional anaesthesia.[13] With the exception of emotional anaesthesia, which was experienced only by the two patients with a history of depression, all patients developed these symptoms. Nevertheless, while the patients continued to take benzodiazepines they had other symptoms associated with benzodiazepine withdrawal—namely, agitation, panic attacks, agoraphobia, hallucinations, flushing, sweating, gastrointestinal disturbances, muscle pains, paresthesiae, and many others. In several cases increased benzodiazepine dosage had been prescribed with temporary alleviation of the symptoms.

The mechanisms of action of benzodiazepines have recently become clearer since the finding of specific benzodiazepine binding sites in the brain, resulting in enhancement of γ-aminobutyric acid activity[14 15] and depression of serotonergic and adrenergic activity in the septo-hippocampal system and perhaps in other limbic pathways.[16] An opioid mechanism may also be concerned.[17] Withdrawal of benzodiazepines (especially if tolerance has occurred[18]) might be expected to be followed by a temporary increase in serotonergic, noradrenergic, and possibly dopaminergic activity in the limbic system, and perhaps decreased activity in opioid systems. At least some of these changes do occur,[18] and benzodiazepine withdrawal is associated with increased output of an anxiety-provoking monoamine oxidase inhibitor, tribulin.[19]

Such changes might account for many of the effects of withdrawal, particularly the anxiety and its somatic concomitants. The muscle stiffness might be due to relative underactivity of γ-aminobutyric acid in brain stem and possibly basal ganglia systems. The perceptual distortions, hallucinations, and disturbance of body image might result from increased serotonergic or perhaps dopaminergic activity at critical brain sites. Moreover, benzodiazepines may also affect endocrine activity, including prolactin release,[20] which might underlie the breast changes noted. Detailed investigations of the metabolic

and hormonal changes in patients undergoing benzodiazepine withdrawal are required, and possibly some of the new anti-benzodiazepines will be useful for such studies.[21]

It is still difficult to explain why benzodiazepine withdrawal should have such protracted features. One possibility is that the drugs remain in the body and exert pharmacological effects long after they are undetectable in the blood. In my patients symptoms persisted for months after the blood concentrations became undetectably low (figure, table II). Secondly, benzodiazepines may induce longlasting changes in the density or sensitivity of one or multiple neurotransmitter receptors in the brain or periphery. Thirdly, benzodiazepines may cause neurological damage, as suggested by Lader for the brain.[22] It is not impossible that the paresthesiae, muscle weakness, and fasciculation, which are so prominent in withdrawal, might be due to a benzodiazepine induced toxic neuropathy. Paresthesiae with a similar distribution have been ascribed to hyperventilation in anxiety neurosis,[8] and blood gas analysis could establish this point in the benzodiazepine withdrawal syndrome—though it would still be necessary to explain why hyperventilation should often continue for so long when other signs of anxiety had receded. Possibly, benzodiazepines cause neuromuscular damage affecting respiratory muscles.

To turn to the practical aspects of benzodiazepine withdrawal, Tyrer *et al* have emphasised that benzodiazepines with short elimination half lives, such as lorazepam, are more likely to produce withdrawal phenomena than those that are eliminated more slowly, such as diazepam.[6] For this reason my patients were changed from lorazepam to diazepam. Some have advocated that withdrawal should be carried out slowly with fortnightly dosage reductions of one eighth of the previous dose,[7] but as most of my patients were already having withdrawal symptoms it seemed likely that such slow progression would merely prolong the agony, and withdrawal within one or two weeks caused few problems. There was no correlation between the severity of withdrawal symptoms and either previous benzodiazepine dosage or plasma concentration of diazepam at the time it was stopped. The rate of fall of plasma diazepam concentration was similar in all cases.

It was noteworthy that patients taking lorazepam tended to crave for their next tablet and also that, to avoid exacerbation of symptoms, the changeover to diazepam needed to be carried out gradually, with substitution of at least 10 mg of diazepam for every 1 mg of lorazepam. Clonidine has been used to control narcotic withdrawal[23] and was moderately but not dramatically helpful in the four patients in whom it was tried in the present series. Propranolol definitely alleviated tremor and muscular twitching but had little effect on subjective features. Haloperidol was effective in stopping hallucinations in the two patients who received it for this purpose. Non-benzodiazepine hypnotics were helpful in insomnia. Further studies are needed on other drugs that would perhaps act more specifically on withdrawal symptoms: partial agonist or antagonists at benzodiazepine receptors[24] or γ-aminobutyric acid analogues such as baclofen[25] are possible candidates.

Finally, these findings show very clearly that benzodiazepine withdrawal is a severe illness. The patients were usually frightened, often in intense pain, and genuinely prostrated. The severity and duration of the illness are easily underestimated by medical and nursing staff, who tend to dismiss the symptoms as "neurotic." In fact, through no fault of their own, the patients suffer considerable physical as well as mental distress. They greatly value close medical contact and support, both in the early withdrawal stages and for a prolonged follow up period. Lay counselling groups for tranquilliser withdrawal can also play an important part in recovery and, because they see more patients undergoing withdrawal than most doctors, can provide a valuable source of information.[26]

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Clinical curio: pinworms and time zones

At 1600 United States central time I examined a 4 year old girl and was surprised to see active mature forms of *Enterobius vermicularis* on her perianal skin. She had left London at 1200 British summer time the previous day so the parasite was acting appropriately for the time zone in which it had presumably been acquired. (1600 United States central time is equivalent to 2300 British summer time.)

The child was a regular transatlantic traveller and usually made a rapid readjustment. Indeed, her sleep pattern and use of energy on the day of examination were more appropriate to American time zones than to British ones. There are two possible explanations for the non-nocturnal behaviour of the parasite. Firstly, the child's true cyclothymic rhythms may not have been reflected in her behaviour and sleep patterns; secondly, *E vermicularis* may follow its own cyclothymic patterns, and an infection acquired in a different time zone may consequently have different times of appearing on the perianal skin. Unfortunately, the demand to treat the child precluded making serial observations of the infestation.—ANNE D WALLING, chairman of the division of community medicine, Kansas.